IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

The Commissioner of Patents & Trademarks
Washington, D.C. 20231
Attn: Box Patent Application

Docket No. SCH 1237 D1
Prior Application: SCH 1237
Examiner: H. Lilling
Art Unit: 1651

Sir: This is a request for filing a
☐ Continuation
☒ Divisional
Under 37 C.F.R. 1.53(b), of prior application Serial No. 08/092,426 filed on July 16, 1993 of Robert E. GARFIELD et al., for TREATMENT OF PREECLAMPSIA, TOXEMIA AND PRETERM LABOR WITH COMBINATION OF PROGESTATIONAL AGENT AND A NITRIC OXIDE SYNTHASE SUBSTRATE AND/OR DONOR

1. ☒ Enclosed are 19 pages of the specification including claims and six sheets of drawings.
2. ☒ Enclosed is a copy of the oath or declaration as originally filed in Serial No. 08/092,426 on 10/18/93 in accordance with 37 C.F.R. §1.63(d).
3. ☒ The filing fee is calculated below:

FOR	NUMBER FILED	NUMBER EXTRA	RATE	FEE
TOTAL CLAIMS	33 - 20	13	$22	286.00
INDEPENDENT CLAIMS	2 - 3	0	$82	0.00
☐ MULTIPLE DEPENDENT CLAIM PRESENTED				
☐ Small Entity Status Claimed under 37 CFR 1.9 and 1.27		BASIC FEE		790.00
Statement(s): ☐ Attached ☐ Filed in Parent		TOTAL FILING FEE		$ 1076.00

4. ☒ The amount of $ 1076.00 is included in the attached check.
   ☒ If a check is not attached, authorization is given to charge the amount indicated in the above sentence to Deposit Account No. 13-3402; two copies of this page being attached for this purpose.
5. ☐ Please charge my Deposit Account No. 13-3402 in the amount of $_____, two copies of this sheet are attached.
6. ☒ The Commissioner is hereby authorized to charge any deficiencies or credit any overpayment in payment of the following fees associated with this communication or otherwise due during the pendency of this application to Deposit Account No. 13-3402.
   ☒ Any filing fees under 37 CFR §1.16 for the presentation of extra claims.
   ☒ Any patent application processing fees under 37 CFR §1.17.
7. ☐ Cancel in this application original claims _____ of the prior application before calculating the filing fee.
8. ☒ Amend the specification by inserting before the first line the sentence:
   -- This is a ☐ continuation, ☒ division, of application Serial No. 08/092,426 filed July 16, 1993. --.
9. ☐ Priority of application No. _____ filed on _____ in _____ is claimed under 35 U.S.C. §119.
10. ☐ The certified copies have been filed in prior application Serial No. ___/_____ filed _____.
11. ☒ The prior application is assigned of record to Board of Regents, The University of Texas System of Austin, Texas and Schering Aktiengesellschaft of Berlin, GERMANY.
12. ☒ The power of attorney in the prior application is to: I. William Millen (19,544); John L. White (17,746); Anthony J. Zelano (27,969); Alan E.J. Branigan (20,565); John R. Moses (24,983); Harry B Shubin (32,004); Brion P. Heaney (32,542); Diana Hamlet-King (33,302); Richard J. Traverso (30,595); Richard E. Kurtz (33,936); John A. Sopp (33,103); John H. Thomas (33,460); Richard M. Lebovitz (37,067) and Luan C. Do (38,434)
    ☒ a. The power appears in the original papers in the prior application.
    ☒ b. Address all future communications to MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
13. ☒ A preliminary amendment is enclosed.
14. ☐ An Information Disclosure Statement is enclosed.
15. ☒ Incorporation By Reference.
    The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 2, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

Date: July 24, 1998

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of		:	
Robert GARFIELD et al.		:	Group Art Unit:
Serial No.:	Unassigned (DIV of 08/092,426)	:	Examiner:
Filed:	HEREWITH	:	

For: **TREATMENT OF PREECLAMPSIA, TOXEMIA AND PRETERM LABOR WITH COMBINATION OF PROGESTATIONAL AGENT AND A NITRIC OXIDE SYNTHASE SUBSTRATE AND/OR DONOR**

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to examination and calculation of the claim fees, please amend the specification of the above-identified application as follows:

In the Claims:

Please amend claims 1-3, 14 and 18 as follows:

1. (Amended.) A method of treating at least one of preeclampsia, [and] accompanied or unaccompanied by preterm labor in a pregnant female mammal, [which comprises] or dysmenorrhea, functional uterine bleeding or hemorrhaging in a non-pregnant female mammal, comprising administering to [the afflicted] a pregnant female in need of said treatment an effective amount of a pharmaceutical composition of claim 14

[(a) an amount of a progestin bioequivalent to 50-300 mg. of injected progesterone and

(b) an amount of nitric oxide synthase substrate, an amount of a nitric oxide donor or both effective to raise the blood level of circulating L-arginine to at least about 1 mmole above the normally 2 to 3 mmolar circulating levels,

optionally, in further combination with one or more of with one or more of agents selected from the group consisting of a cyclooxygenase inhibitor, a PGI_2-mimetic, a thromboxane (TXA_2) inhibitor, a compound possessing TXA_2-agonistic and TXA_2-inhibiting properties, a compound possessing TXA_2-antagonistic and PGI_2-mimetic activities, and a TXA_2-antagonist which amounts being effective to ameliorate the symptoms thereof].

2. (Amended.) The method of claim 1, wherein the female mammal is a human suffering from preeclampsia unaccompanied by preterm labor.

3. (Amended.) The method of claim 1, wherein the female mammal is a human [who has exhibited] suffering from preeclampsia and is also exhibiting symptoms of [or is a candidate for] preterm labor.

14. (Amended.) A pharmaceutical composition comprising an admixture of

(a) a progestin and

(b) a nitric oxide synthesis substrate, a nitric oxide donor or both,

and, optionally, [also]

(c) at least one of a cyclooxygenase inhibitor, a PGI_2-mimetic, a thromboxane (TXA_2) inhibitor, a PGI_2-mimetic, a thromboxane (TXA_2) inhibitor, a compound possessing [TXA_2-agonistic] PGI_2-agonistic and TXA_2-inhibiting properties, a compound possessing TXA_2-antagonistic and PGI_2-memetic activities, and a TXA_2 antagonist, in amounts effective to ameliorate the symptoms of preeclampsia[, toxemia or] accompanied or unaccompanied by preterm labor in a pregnant female mammal[when administered thereto in an amount effective provide an amount of the progestin bioequivalent to 50-300 mg. of injected progesterone and an amount of the nitric oxide synthase substrate, nitric oxide donor or both effective to raise the blood level of circulating L-arginine to at least about 1 mmole above the normally 2 to 3 mmolar circulating levels or raise the nitric oxide donor levels to about 1 to 1000 nmolar].

18. (Amended.) The composition according to claim 17, wherein the nitric oxide donor is sodium nitroprusside, nitroglycerin, [glyceryltrinitrie] glyceryltrinitrate, SIN-1, [isosorbidmononitrite] isosorbidmononitrate or [isosorbiddinitrite] isosorbiddinitrate.

Please add the following new claims:

-- **22.** A method of claim 4, wherein the amount of nitric oxide synthase substrate is effective to raise the blood level of circulating L-arginine to at least about 1 mmole above the normal circulating level of L-arginine.

23. A method of claim 6, wherein the amount of nitric oxide donor is effective to provide a blood level of such donor of about 1-1000 nmole.

24. A method of claim 1, further comprising administering an effective amount of (c).

25. A method of claim 1, wherein the female mammal is human, and the amount of progestin is bioequivalent in said treatment to 50-300 mg of injected progesterone.

26. A method of claim 1, wherein the female mammal is human, and the amount of nitric oxide synthase substrate is effective to raise the blood level of circulating L-arginine to at least about 1 mmole above the normal circulating level of 2 to 3 nmolar.

27. A method of claim 6, wherein the female mammal is human, and the amount of nitric oxide donor is effective to provide a blood level of nitric oxide donor of about 1-1000 nmole.

28. A composition of claim 14, further comprising administering effective amounts of one or more agents selected from the group consisting of a cyclooxygenase inhibitor, a PGI_2-mimetic, a thromboxane (TXA_2) inhibitor, a compound possessing PGI_2-agonistic and TXA_2-inhibiting properties, a compound possessing TXA_2-antagonistic and PGI_2-mimetic activities, and a TXA_2-antagonist.

29. A composition of claim 14, wherein the amount of progestin is bioequivalent to 50-300 mg of injected progesterone.

30. A composition of claim 15, wherein the amount of nitric oxide synthase substrate is effective to raise the blood level of circulating L-arginine to at least about 1 mmole above the normal circulating level of 2 to 3 nmolar.

31. A composition of claim 17, wherein the amount of nitric oxide donor is effective to provide a blood level of nitric oxide donor of about 1-1000 nmole.

32. The method of claim 1, wherein the female mammal is a human suffering from dysmenorrhea, functional uterine bleeding or hemorrhaging.

33. A method of inhibiting the nitric oxide dependent contractility of the uterus of a non-pregnant female mammal or a pregnant female mammal suffering from preeclampsia accompanied or unaccompanied by preterm labor, comprising administering an effective amount of a pharmaceutical composition of claim 14.--

REMARKS

Withdrawal of Previous Election and New Election

In accordance with M.P.E.P. § 819, Applicants hereby expressly indicate that a change in election is desired. Applicants now elect the pharmaceutical composition claims. However, it is noted that all of the method claims are dependent on the product (pharmaceutical composition) claims, and if a restriction is made, rejoinder of the method claims will be required when the product claims are allowed.

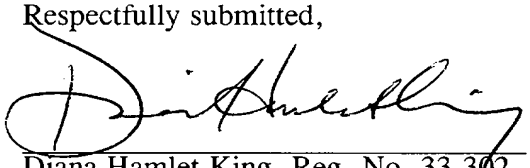
Moreover, insofar as the Examiner may restate a requirement for election of species in response to the above amendments and election, Applicants elect a pharmaceutical composition comprising progesterone and a nitric oxide donor, e.g., nitroglycerin. Claims 14-21 and 28-31 (e.g., because (b) may be both a nitric oxide donor and nitric oxide synthase substrate) read on the elected species, as well as all of the method claims. If these claims are found allowable, the Examiner is again reminded that consideration of the **entire** scope of the claims is required.

Potential rejection under § 103 over Harrison

It is respectfully submitted that the teaching of Harrison et al. (cited in the parent application) does not anticipate nor render obvious any of the present pharmaceutical composition claims, and in particular does not render obvious any of the method claims insofar as they relate to pregnant females suffering from preeclampsia, with or without concurrent preterm labor. Harrison clearly does not read on preterm labor as part of the preeclampsia syndrome, and in fact, explicitly teaches away from using tocolytic agents (for labor inhibition) in the case of preeclampsia: see col. 2, lines 4-13 ("contraindications such as eclampsia, preeclampsia ...").

In view of the above remarks and amendments, it is respectfully submitted that the application is in condition for allowance, which action is respectfully requested.

Respectfully submitted,



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TREATMENT OF PREECLAMPSIA AND PRETERM LABOR WITH COMBINATION OF PROGESTATIONAL AGENT AND A NITRIC OXIDE SYNTHASE SUBSTRATE AND/OR DONOR

Background of the Invention

This invention relates to a method for the treatment of preeclampsia and of preterm labor with the combination of a progestational agent and a nitric oxide synthase substrate, a nitric oxide donor or both, alone or in further combination with one or more of a cyclooxygenase inhibitor, a PGI_2-mimetic, a thromboxane (TXA_2) inhibitor, A compound possessing TXA_2-agonistic and TXA_2-inhibiting properties, a compound possessing TXA_2 antagonistic and PGI_2-memetic activities, and a TXA_2 antagonist, and to pharmaceutical compositions comprising such a combination.

Preeclampsia, toxemia or eclampsia of pregnancy can be a significant health problem during pregnancy and they are the leading causes of fetal growth retardation, fetal mortality and morbidity, premature birth and maternal mortality. The etiology of the disease is largely unknown and effective therapy is not available. Preeclampsia of pregnancy is characterized by a triad of hypertension, pathological edema and proteinuria. This disease affects 6 to 10% of all pregnancies.

Recently, nitric oxide has been shown to be endothelium derived relaxing factor (EDRF) from the endothelium of blood vessels. Nitric oxide is considered to be a major mediator in the control of vascular reactivity. Nitric oxide is synthesized from L-arginine by nitric oxide synthase located in endothelial cells. Nitric Oxide can also be generated by application of various nitric oxide donors such as sodium nitroprusside, nitroglycerin, glyceryl trinitrite, SIN-1, isosorbid mononitrite, isosorbid dinitrite, etc.

Treatment of pregnant rats with nitric oxide synthase inhibitors, which are analogues of L-arginine (such as L-NAME, N^G- nitro-L-arginine methyl ester) results in

elevated blood pressure, fetal retarded growth and proteinuria. Thus, inhibition of nitric oxide synthesis produces conditions and symptoms identical to preeclampsia of pregnancy and establishes that preeclampsia is the direct result of the decrease in nitric oxide synthesis and/or a change in the regulation of vascular tone. These conditions give rise to increased blood pressure, decreased blood flow to the fetus, retarded fetal development and proteinuria. Agents which raise nitric oxide levels therefore are useful in the treatment of preeclampsia of pregnancy. Since nitric oxide donors also reduce contractility of the uterus during pregnancy, nitric oxide donors are also useful for use in preterm labor.

The nitric oxide effects on smooth muscle depend upon the activation of guanylate cyclase and generation of cGMP to produce relaxation and this step is progesterone dependent. Thus, combinations of nitric oxide donors with progesterone are particularly efficacious for the treatment of preeclampsia and of preterm labor.

EP 0 441 119 A2 discloses the use of L-arginine in the treatment of hypertension and other vascular disorders. It suggests that the mechanism by which L-arginine is effective for this purpose is because it may be the physiological precursor of "the most powerful endothelial-derived releasing factor, nitric oxide." The use of L-arginine in combination with other pharmaceutically active agents is not discussed in this publication.

Objects of the Invention

It is an object of the invention to provide a method for the prevention and treatment of preeclampsia with a combination of a progestational agent and a nitric oxide substrate and/or donor.

It is another object to provide such a method in which a progestational agent is used in combination with

a nitric oxide substrate and/or donor for the prevention and treatment of preeclampsia.

It is a further object to provide a method for the prevention and treatment of preterm labor using a progestational agent in combination with a nitric oxide substrate and/or donor.

A further object is the provision of pharmaceutical compositions useful in practicing the methods of this invention.

Other objects will be apparent to those skilled in the art to which this invention pertains.

Summary of the Invention

In a method aspect, this invention relates to a method of treating at least one of preeclampsia and preterm labor in a pregnant female which comprises administering to a pregnant female manifesting the symptoms thereof, (a) a progestational agent and (b) one or both of a nitric oxide synthase substrate and a nitric oxide donor, alone or in further combination with one or more of a cyclooxygenase inhibitor, a PGI_2-mimetic, a thromboxane (TXA_2) inhibitor, a compound possessing TXA_2-agonistic and TXA_2-inhibiting properties, a compound possessing TXA_2-antagonistic and PGI_2-memetic activities, and a TXA_2 antagonist, in amounts effective to ameliorate the symptoms thereof, the amount of the progestational agent administered being bioequivalent to 50-300 mg. of injected progesterone and the amount of the nitric oxide synthase substrate, nitric oxide donor or both being effective to, respectively, either raise the blood level of circulating L-arginine in a pregnant female to whom the composition is administered to at least about 1 mmole above the normally 2 to 3 mmolar circulating levels or raise nitric oxide donor levels to about 1 to 100 nmolar (nanamolar).

In another method aspect, this invention relates to a method of treating preterm labor in a pregnant female which comprises administering to a pregnant female

manifesting the symptoms thereof, amounts of (a) a progestational agent and (b) at least one of a nitric oxide synthase substrate and a nitric oxide donor effective to terminate the preterm labor, alone or in further combination with one or more of a cyclooxygenase inhibitor, a PGI_2-mimetic, a thromboxane (TXA_2) inhibitor, a compound possessing TXA_2-agonistic and TXA_2-inhibiting properties, a compound possessing TXA_2-antagonistic and PGl_2-memetic activities, and a TXA_2 antagonist, the amount of the progestational agent administered being bioequiva-lent to 50-300 mg. of injected progesterone and the amount of the nitric oxide synthase substrate, nitric oxide donor or both being effective to, respectively, either raise the blood level of circulating L-arginine in a pregnant female to whom the composition is administered to at least about 1 mmole above the normally 2 to 3 mmolar circulating levels, or raise nitric oxide donor levels to about 1 to 100 nmolar.

In a product aspect, this invention relates to a pharmaceutical composition comprising (a) a progestational agent and (b) at least one of a nitric oxide synthase substrate and a nitric oxide donor, alone or in further combination with one or more of a cyclooxygenase inhibitor, a PGI_2-mimetic, a thromboxane (TXA_2) inhibitor, a compound possessing TXA_2-agonistic and TXA_2-inhibiting properties, a compound possessing TXA_2-antagonistic and PGl_2-memetic activities, and a TXA_2 antagonist, with the amount of the progestational agent per unit dosage being bioequivalent to 50-300 mg. of injected progesterone and the amount of the nitric oxide synthase substrate, a nitric oxide donor or both per unit dosage being effective to, repsectively, either raise the blood level of circulating L-arginine to at least about 1 mmole above the normally 2 to 3 mmolar circulating levels or raise the nitric oxide donor levels to about 1 to 1000 nmolar.

Detailed Disclosure

The methods of this invention treat one or more of preeclampsia and preterm labor in a pregnant female mammal, preferably a human, who is manifesting the symptoms thereof or who is a high risk candidate for doing so, e.g., as determined by the progress of a present or previous pregnancy.

Because these abnormal conditions of pregnancy are produced by or aggravated by subnormal nitric oxide synthesis, both nitric oxide synthase substrates, e.g., L-arginine, and nitric oxide donors, e.g., sodium nitroprusside, nitroglycerin, glyceryl trinitrate, SIN-1, isosobid mononitrate and isosorbid dinitrate, are useful for ameliorating the symptoms thereof and, in one aspect of the method of this invention, a combination of both are employed.

A synergistic effect is achieved when a progestational agent is administered concurrently with the nitric oxide substrate and/or nitric acid donor.

Thus, the method aspect of this invention and the pharmaceutical composition aspect of this invention employs a combination of (a) a progestational agent, e.g., progesterone, and (b) either or both of a nitric oxide donor and a nitric oxide synthase substrate and, optionally, (c) one or more of a cyclooxygenase inhibitor, e.g., aspirin; a PGI_2-mimetic, e.g., iloprost and cicaprost; a thromboxane (TXA_2) inhibitor, e.g., dazoxiben hydrochloride (benzoic acid, 4-[2-(1H-imadazol1-yl)-ethoxy]-, monohydrochloride; UK 37248), dazmegrel (1H-indole-1-propanoic acid, 3-(1H-imidazol-1-ylmethyl)-2-methyl-; UK 3885), ozagrel (2-propenoic acid, 3-[4-(1-H-imidazol-1-ylmethyl)phenyl]-; OKY-046) and pirmagrel (imidazo[1,5-a]pryidine-5-hexanoic acid; CGS-13080); a compound possessing TXA_2-agonistic and TXA_2-inhibiting properties, e.g., ridogrel (pentanoic acid, 5-[[[3-pyridinyl[3-(trifluoromethyl)phenyl]methylene]-amino]oxy]-; R-68070) and labogrel (6-heptenoic acid, 7-phenyl-7-(3-

pydridinyl)-; a compound possessing TXA_2-antagonistic and PGI_2-memetic activities, e.g., 5-heptenoic acid, 7-[3-[[(diphenylmethoxy)-imino]-bicyclo,[2.2.1]hept-2-yl]-; EP 035-rac) and 5-heptenoic acid, 7-[3-[[(diphenylmethoxy)-imino]methyl]biclo[2.2.2]-oct-5-en-2-yl]- (EP 157); and a TXA_2 antagonist, e.g., 5-heptenoic acid, 7-[3-[[2-(phenylamino)carbonyl]-hydrazino]methyl]7-oxabicyclo[2.2.1]hept-2-yl]-, 1S[1.alpha.,2.alpha.(Z),3.alpha.,4.alpha.]]- (SQ 29548); benzenepropanoic acid, 2-[[3-4[(pentylamino)carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-ylmethyl}- (BMS 180291); acetic acid, [4-[2-[(phenylsulfonyl)amino]-ethyl]penoxy]- (sultroban, BM-13177); benzeneacetic acid, 4-[2-[[[4-chlorophenyl)sulfonyl]amino]ethyl]- (daltroban, BM-13505); (S-145 rac); 5-hexenoic acid, 6-[3-[[[(4-bromophenyl)sulfonyl]amino]methyl]bicyclo[2.2.1]hep-2-yl]-, decyl ester, [IS[1.alpha.2.alpha.2.alpha.(Z),-3.beta.,4.alpha.]]- (ONO 8809); 9H-carbazole-9-propanoic acid, 3-[[(4-fluorophenyl)sulfonyl]amino]-1,2,3,4-tetra-hydro-, (R)- (bay-u-3405); and (4Z)-6-[(5S)-5-(4-chlor-phenylsulfonyl(aminomethyl)-cycloent-1-enyl]4-hexenoic acid (ZU 154343).

Examples of combinations of active agents which can be administered concurrently with a nitric oxide substrate and/or a nitric oxide donor and a progesterone (or other progestational agent) are low dose (e.g.,10-100 mg) of aspirin (or other cyclooxygenase inhibitor; PGI_2-mimetics (e.g., iloprost, cicaprost); combinations of a PGI_2-mimetic and low dose aspirin.

Examples of dosage ranges of typical NO-substrates and NO-donors (per os) are:

	total dose:
L-Arginine	500 mg - 10 g p.o.
Sodium Nitroprusside	range 500-2000 ug/kg/day
Nitroglycerin	0.5-10 mg
Isosorbid mononitrate	10-100 mg
Isosorbid dinitrate	10-100 mg

The following are typical oral dosage ranges active agents of the progestin and the optional other active agents concurrently administered with the nitric oxide substrate or donor:

Progestins: A daily dose bioequivalent to 50-300 mg of progesterone/day, e.g., an injectable suspension of medroxyprogersterone acetate to provide a weekly dose of thereof of 100-1000 mg or tablets or dragees providing an oral dose thereof of 5-10 mg/day; an injectable solution of hydroxyprogesterone caproate which provides a weekly dose of 250-500 mg; tablets, capsules or dragees of northindrone acetate which provide a daily dose of 5-20 mg.

Cicaprost: 5-100 ug/kg/day p.o.

Aspirin: 10-100 mg/kg/day p.o.

The pharmacologically active agents employed in this invention can be administered in admixture with conventional excipients, i.e., pharmaceutically acceptable liquid, semi-liquid or solid organic or inorganic carriers suitable, e.g., for parental or enteral application and which do not deleteriously react with the active compound in admixture therewith. Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions, alcohols, vegetable oils, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxy methylcellulose, polyvinyl pyrrolidone, etc. The pharmaceutical preparations can be sterilized and if desired mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, flavoring and/or aromatic substances and the like which do not deleteriously react with the active compounds.

For parental application, particularly suitable are solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions, or implants, including suppositories. Ampoules are convenient unit dosages.

In a preferred aspect, the composition of this invention is adapted for ingestion.

For enteral application, particularly suitable are unit dosage forms, e.g., tablets, dragees or capsules having talc and/or a carbohydrate carrier or binder or the like, the carrier preferably being lactose and/or corn starch and/or potato starch; particulate solids, e.g., granules; and liquids and semi-liquids, e.g., syrups and elixirs or the like, wherein a sweetened vehicle is employed. Sustained release compositions can be formulated including those wherein the active compound is protected with differentially degradable coatings, e.g., by microencapsulation, multiple coatings, etc.

Suitable for oral administration are, inter alia, tablets, dragees, capsules, pills, granules, suspensions and solutions. Each unit dose, e.g., each tablespoon of liquid or each tablet, or dragee contains, for example, 5-5000 mg of each active agent.

Solutions for parenteral administration contain, for example, 0.01 - 1% of each active agent in an aqueous or alcoholic solution.

The nitric oxide substrate and/or donor can be administered as an admixture with the progestational agent and any other optional active agent or as a separate unit dosage form, either simultaneously therewith or at different times during the day from each other.

The combination of active agents is preferably administered at least once daily (unless administered in a dosage form which delivers the active agents continuously) and more preferably several times daily, e.g., in 2 to 6 divided doses. The typical dose is about 0.5 to 1000 mg of each active agent, although some less active agents, e.g., L-Arginine, require much higher oral dosages, e.g., 500 to 10,000 mg, and others, e.g., sodium nitroprusside, require lower doses, e.g., 500-2,000 ug/kg/day. Doses for nitroglycerine typically are orally 2.5 mg 2 x daily; sublingually, 0.8 mg 1-4 x dialy; and

transdermally, 0.2-0.4 mg/hr. Since the LD_{50} dosages of most of these active agents is known in the prior art, a lower dosage regimen can be initiated and the dosage increased until a positive effect is achieved or a higher dosage regimen can initially be employed, e.g., in a crisis situation, and the dosages regulated downward as relief from the symptoms is achieved.

In humans, both L-arginine and progesterone (or bioequivalent of another progestin) should be given in a ratio which produces blood plasma levels of about 1-5mMol/ml and 300-1,000 ng/ml (0.9-3μMol/l), respectively. The NO-donor, e.g., sodium nitroprusside, should be given with the progesterone (or bioequivalent of another progestin) in a ratio producing blood plasma levels of about 1-10 μMol/l and 300-1,000 ng/ml (0.9-3μMol/l), respectively.

Brief Description of the Drawings

With reference to the drawings,

FIGURE 1 is a series of strip chart recordings showing the effect of L-arginine on spontaneously contracting uterine strips from rat on day 18 of gestation;

FIGURE 2: Dose-dependent relaxation effects of L-arginine (0.1 mM to 10 mM) on spontaneously contracting uterine strips from rats at different stages of gestation, during delivery adn post partum. The tissues were obtained on days 17-22 (d17, d18, d19 and d22) of gestation, on day 22 (d22 del) during spontaeous delivery (1-3 pups delivered), or on 1 (d1pp) and 2 (d2pp) days postpartum. The duration of complete inhiition of spontaneous uterine contractiosn are dose-dependent. Data are analyzed by repeated measures ANOVA on seven groups. The effects of L-arginine from concentrations of 1 mM are significantly ($P<0.01$) decreased durign spontaeous delivery at term adn postpartum, compared to all other times. Each data point represent mean ± S.E.M.

The total number of strips studied at each time period was 8-16 from 4-6 animals per group.

FIGURE 3: Dose response effects of L-arginine (0.6 mM to 10 mM) on the spontaeous contractility of uterine strips from ovariectomized adult rats. Animals received s.c. injection of 1 ug estradiol - 17b (OVX + E), 2 mg progesterone (OVX + P), estraodiol and progesterone (OVZ + E + P) in sesame oil or oil alone (OVX + Oil) for 3 days prior to contractility measurements. Values are mean ± SEM for 4 strips from each animal from 4 rats per group. Data are analyzed by repeated measures ANOVA on four groups. *P<0.05 OVX + P vs OVX + E.

FIGURE 4: 8-bromo-cGMP dose relaxation-response curves for uterine tissues from rats delivering, spontaeously at term (DEL), preterm with ZK299 (PRETERM DEL) and nondelivering (NONDEL) on day 18 of gestation. Each point represent means ± SEM for 4 strips from each animal from 4 rats per group.

FIGURE 5 is a bar chart which shows the effect on blood pressure of test animals of 50 mg of the hypertensive agent L-NAME, alone or in combination with one or both of L-arginine and progmesterone (R-5020); and

FIGURE 6 is bar chart which shows the effect in the same experiments on pup weights of these compounds.

Discussion of the Drawings

The strip chart recordings of Figure 1 show that the application of L-arginine (1-3 mM) (A, B, E), sodium nitroprusside (5 mM)(C), nitric oxide (0.1 mM) (D) to muscle baths produced substantial relaxations. The effects of L-arginine were reversed by L-NAME (3 mM)(B) and methylene blue (0. mM)(E). These ar etypical recordings of 8-16 strips from 6 animals in each group. Each upstroke from baseline represents a contraction.

The strip chart recording of Figure 1C show that the application of sodium nitroprusside (SNP) caused sustained relaxation in spontaneously contracting uterine strips after a lag period and that tissues in the relax

state were responsive to potassium chloride. Similar recordings of 12 uterine strips from 4 animals were obtained.

The strip chart recording in Figure 1D show the relaxation produced by authentic nitric oxide gas (0.1 mM). Similar recordings were obtained from 8 strips from 4 animals.

The strip chart recordings of Figure 1E show that L-arginine (1 mM) produced relaxation of spontaneously contracting tissues and these effects were repeatable in the same strip (as in Fig. 1A) and that the relaxation effect of L-arginine (1 mM) was abolished by methylene blue (0.1 mM) when added before the application of L-arginine (B).

In the experiments whose results are shown by the graph of Figure 2, the tissues were obtained on days 17-22 (d17, d18, d19 and d22) of gestation, on day 22 (d22 del) during spontaneous delivery (1-3 pups delivered), or on 1 (d1pp) and 2 (d2pp) days postpartum. The duration of complete inhibition of spontaneous uterine contractions are dose-dependent. The effects of L-arginine from concentrations of 1 mM are significantly ($P<0.01$) decreased during spontaneous delivery at term and postpartum, compared to all other times. Each data point represent mean ± S.E.M. The total number of strips studied at each time period was 8-16 from 4-6 animals per group.

In the experiments whose results are shown by the graph of Figure 3, nonpregnant ovariectomized rats received s.c. injection of 1 ug estradiol-17-ß (OVX + E), 2 mg progesterone (OVX + P), estradiol and progesterone (OVX + E + P) in sesame oil or oil alone (OVX + Oil) for 3 days prior to contractility measurements. Values are mean ± SEM for 4 strips from each animal from 4 rats per group. *$P<0.05$ OVX + P vs OVX + E.

The charge of Figure 4 shows 8-bromo-cGMP dose relaxation-response curves for uterine tissues from rats

delivering, spontaeously at term (DEL), preterm with ZK299 (PRETERM DEL) and nondelivering (NONDEL) on day 18 of gestation. Each point represent means ± SEM for 4 strips from each animal from 4 rats per group.

The data in Table 1 below show the effects of L-NAME infusion on blood pressure (mm Hg) in pregnant rats.

TABLE 1

	Blood Pressure (mm Hg)		
		L-NAME	
Gestation day	CONTROL	25 mg/day	50 mg/day
Day 15	121 ± 3[a]	119 ± 2[a]	123 ± 3[a]
Day 18	119 ± 3[a]	144 ± 4[b]	166 ± 2[c]
Day 22	120 ± 5[a]	146 ± 2[b]	168 ± 3[c]

Means with different superscripts differ significantly ($P<0.05$)

The data in Table 2 below show the delivery and the pups delivered of L-NAME infusion to pregnant rats.

TABLE 2

	CONTROL	L-NAME	
		25 mg/day	50 mg/day
Day of Delivery	22.3 ± 0.2	22.4 ± 0.2	22.7 ± 0.2
Total # of pups	59	65	56
# of dead pups	2	5	10
Weight of pups	6.32 ± 0.05[a]	5.05 ± 0.08[b]	4.56 ± 0.10[c]
Total # of animals	8	9	10

Means with different superscripts differ significantly ($P<0.05$).

Another experiment using L-NAME-induced" pre-eclampsia" showed that treatment with L-arginine alone partially reduced blood pressure (Figure 5). Similarly, animals treated with L-NAME and R 5020 (promegestone), a progestational agent with no antimineralocorticoid effect

or other antagonistic or agonistic properties, also partinally reduced L-NAME-induced hypertension. As also shown in Figure 5, when the same doses of L-arginine and R 5020 were given simultaneously, their combined effect lowered blood pressure to normal levels.

Additionally, evaluation of fetal weights in the same animals treated as described above, showed intrauterine fetal retardation (decreased weight of pups), typical preeclamptic fetuses (Figure 6). Treatment of the "preeclamptic" groups of animals with either L-arginine alone or R 5020 alone slightly but statistically significant, elevated fetal weights. As also shown in Figure 6, the combined effect of the two compounds administered together significantly elevated fetal weight above that observed with either compound alone, a highly significant advantage to survival of the fetus under these conditions.

It can be concluded from these studies that the combined treatment of L-arginine with a progestational agent whose activity is "pure", like R 5020 provides results which cannot be achieved with either type of drug alone. The studies show that the basis for this effectiveness lies in the ability of the progestional agent to increase the effectiveness of nitric oxide (or L-arginine, the substrate of nitric oxide) to dilate bood vessels and thereby lower blood pressure as well as increase fetalmaternal profusion, thereby increasing fetal weight.

The combined effect of the combination of these agents is surprisingly dramatic and, more importantly, the significant fetal and maternal effects observed with treatment with the combination. Prior medical evidence does not suggest that the combination would provide these advantages, because the basis for them is not the simple combination of two agonistic compounds but instead is the sensitizing of nitric oxide provided by the progestin. The studies clearly indicate that progestins increase the

effector system for nitric oxide (not increase nitric oxide synthesis).

The method of treatment employed in this invention can also be employed for the treatment of hypertension (in both females and males), climacteric disorders (hot flushes, mood swings) in menopausal women, thrombotic disorders, menstrual disorders (dysmenorrhea, functional uterine bleeding), and hemorrhage, etc., following the dosage regime described herein.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the disclosure in any way whatsoever.

The entire disclosure of all applications, patents and publications, cited above and below are hereby incorporated by reference.

Examples

Example 1 - Treatment of Preeclampsia

To a pregnant human female (ca 20-40 years; 60-80 kg) usually in her second half of pregnancy and displaying the symptoms of preeclampsia, including hypertension (above 140 mm systolic and above 90 mm diastolic), edema and protein-uria, administer 0.5 to 20 g of L-arginine and 200 mg of micronized progesterone per os daily in three divided doses until the symptoms are ameliorated. Thereafter, administer 0.5 to 5 mg of L-arginine and 60 mg of progesterone per os daily whenever the diastolic pressure rises above 80 mm; with increasing doses of L-argininine to from 5 to 20 mg daily until remission of the symptoms again occurs.

Example 2 - Treatment of preeclampsia

To a human female comparable to and displaying the same symptoms as the one described in Example 1, administer daily 2 x 2.5 mg of nitroglycerine and 200 mg

of progesterone following the same protocol, until the symptoms are ameliorated.

Example 3 - Treatment of Preterm Labor

To a human female in her sixth month of pregnancy and displaying symptoms of a threatened spontaneous abortion, including blood spotting and periodic uterine spasms, administer daily 17 g of L-arginine and 50 mg of progesterone per os daily in three divided doses until the symptoms are ameliorated. Thereafter, administer 5 g of L-arginine and 50 mg of progesterone per os daily with increasing doses to 20 g of L-arigine daily until remission of the symptoms again occurs.

Example 5 - Treatment of Preterm Labor

To a pregnant human female comparable to and displaying the same symptoms as the one described in Example 3, administer daily 2 x 25 mg of nitroglycerine and up to 180 mg of progesterone, following the same protocol, until the symptoms are ameliorated.

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

WHAT IS CLAIMED IS:

1. A method of treating at least one of preeclampsia and preterm labor in a pregnant female mammal, which comprises administering to the afflicted female (a) an amount of a progestin bioequivalent to 50-300 mg. of injected progesterone and (b) an amount of nitric oxide synthase substrate, a nitric oxide donor or both effective to raise the blood level of circulating L-arginine to at least about 1 mmole above the normally 2 to 3 mmolar circulating levels, optionally, in further combination with one or more of with one or more of a cyclooxygenase inhibitor, a PGI_2-mimetic, a thromboxane (TXA_2) inhibitor, a compound possessing TXA_2-agonistic and TXA_2-inhibiting properties, a compound possessing TXA_2-antagonistic and PGl_2-memetic activities, and a TXA_2 antagonist, which amounts being effective to ameliorate the symptoms thereof.

2. The method of claim 1, wherein the female mammal is a human suffering from preeclampsia.

3. The method of claim 1, wherein the female mammal is a human who has exhibited or is a candidate for preterm labor.

4. The method of claim 1, wherein the female mammal is a human and a nitric oxide synthase substrate is administered thereto.

5. The method of claim 4, wherein the substrate is L-arginine.

6. The method of claim 1, wherein the female mammal is a human and a nitric oxide donor is administered thereto.

7. The method of claim 6, wherein the nitric oxide donor is sodium nitroprusside, nitroglycerin, glyceryltrinitrie, SIN-1, isosorbidmononitrite or isosorbiddinitrite.

8. The method of claim 6, wherein the nitric oxide donor is administered orally.

9. The method of claim 1, wherein the female mammal is a human and the nitric oxide substrate or donor is administered thereto in combination with a cyclooxygenase inhibitor.

10. The method of claim 9, wherein the inhibitor is aspirin.

11. The method of claim 1, wherein the female mammal is a human and the nitric oxide substrate or donor is administered thereto in combination with a PGI_2-mimetic.

12. The method of claim 11, wherein the PGI_2-mimetic is iloprost or cicaprost.

13. The method of claim 1, wherein the female mammal is a human and the progestin administered thereto is progesterone.

14. A pharmaceutical composition comprising an admixture of (a) a progestin and (b) a nitric oxide synthesis substrate, a nitric oxide donor or both, and optionally, also at least one of a cyclooxygenase inhibitor, a PGI_2-mimetic, a thromboxane (TXA_2) inhibitor, a PGI_2-mimetic, a thromboxane (TXA_2) inhibitor, a compound possessing TXA_2-agonistic and TXA_2-inhibiting properties, a compound possessing TXA_2-antagonistic and PGl_2-memetic activities, and a TXA_2 antagonist, in amounts effective to ameliorate the symptoms of

preeclampsia, toxemia or preterm labor in a pregnant female mammal when administered thereto in an amount effective provide an amount of the progestin bioequivalent to 50-300 mg. of injected progesterone and an amount of the nitric oxide synthase substrate, nitric oxide donor or both effective to raise the blood level of circulating L-arginine to at least about 1 mmole above the normally 2 to 3 mmolar circulating levels or raise the nitric oxide donor levels to about 1 to 1000 nmolar.

15. The composition according to claim 14, wherein (b) is a nitric oxide synthesis substrate.

16. The composition according to claim 15, wherein the nitric oxide synthesis substrate is L-arginine.

17. The composition according to claim 14, wherein (b) is a nitric oxide donor.

18. The composition according to claim 17, wherein the nitric oxide donor is sodium nitroprusside, nitroglycerin, glyceryltrinitrie, SIN-1, isosorbidmononitrite or isosorbiddinitrite.

19. The composition according to claim 17, which comprises a cyclooxygenase inhibitor.

20. The composition according to claim 17, which comprises a PGI_2-mimetic.

21. The composition according to claim 17, which comprises a thromboxane inhibitor.

ABSTRACT OF THE DISCLOSURE

Preeclampsia and preterm labor in a pregnant female mammal are treated by administering thereto a combination of a progestin and a nitric oxide synthase substrate, a nitric oxide donor or both, optionally in further combination with one or more of a cyclooxygenase inhibitor, a PGI_2-mimetic, a thromboxane (TXA_2) inhibitor, a compound possessing TXA_2-agonistic and TXA_2-inhibiting properties, a compound possessing TXA_2-antagonistic and PGI_2-memetic activities, and a TXA_2 antagonist.

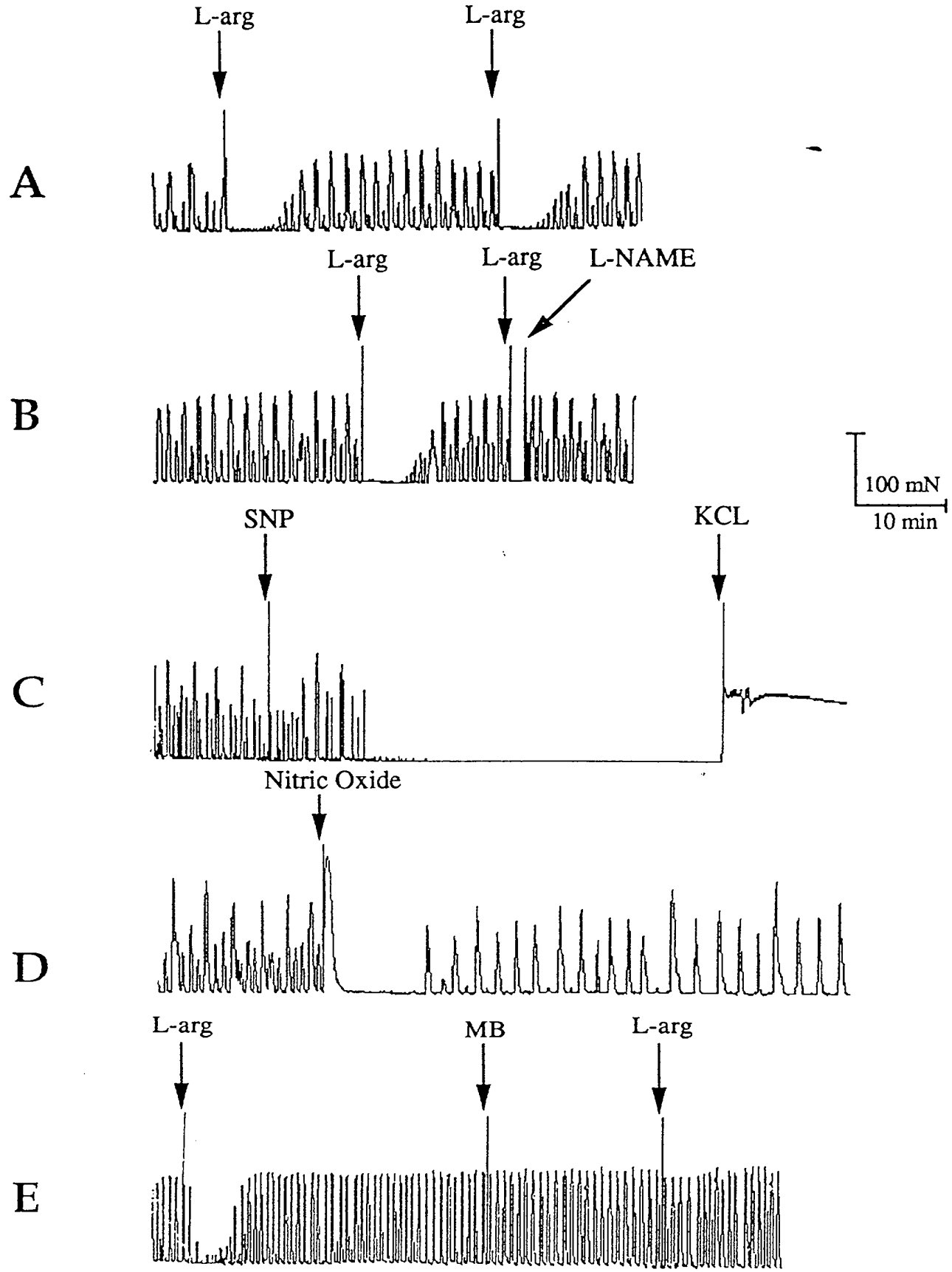
L-arg
L-arg
A
L-arg
L-arg
L-NAME
B
100 mN
10 min
SNP
KCL
C
Nitric Oxide
D
L-arg
MB
L-arg
E

Figure 1

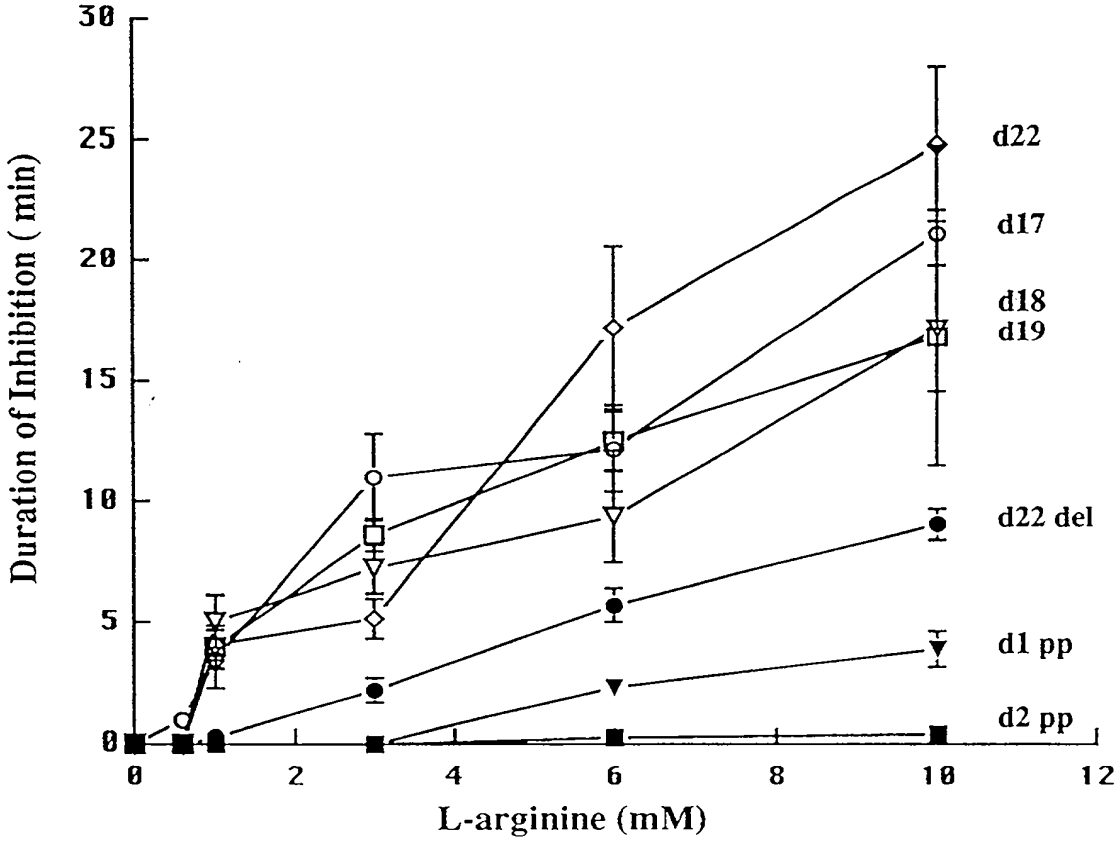
Duration of Inhibition (min)
30
25
20
15
10
5
0
0
2
4
6
8
10
12
L-arginine (mM)
d22
d17
d18
d19
d22 del
d1 pp
d2 pp

Figure 2

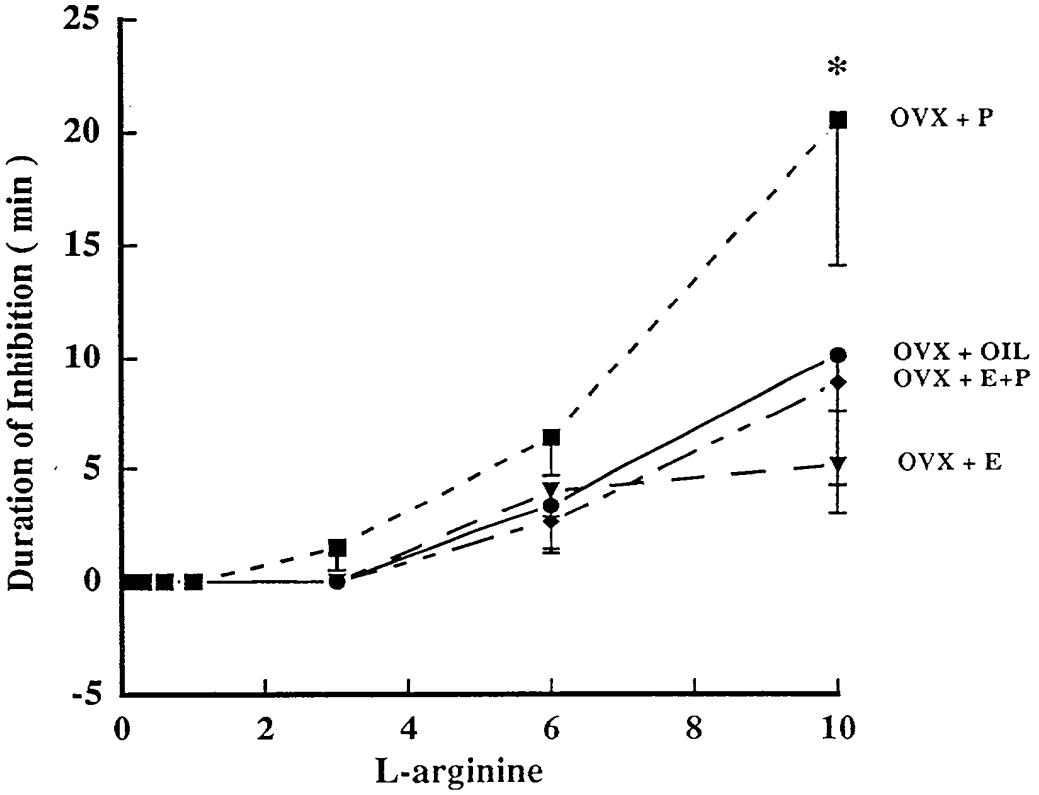
25
20
15
10
5
0
-5
0
2
4
6
8
10
Duration of Inhibition (min)
L-arginine
*
OVX + P
OVX + OIL
OVX + E+P
OVX + E

Figure 3

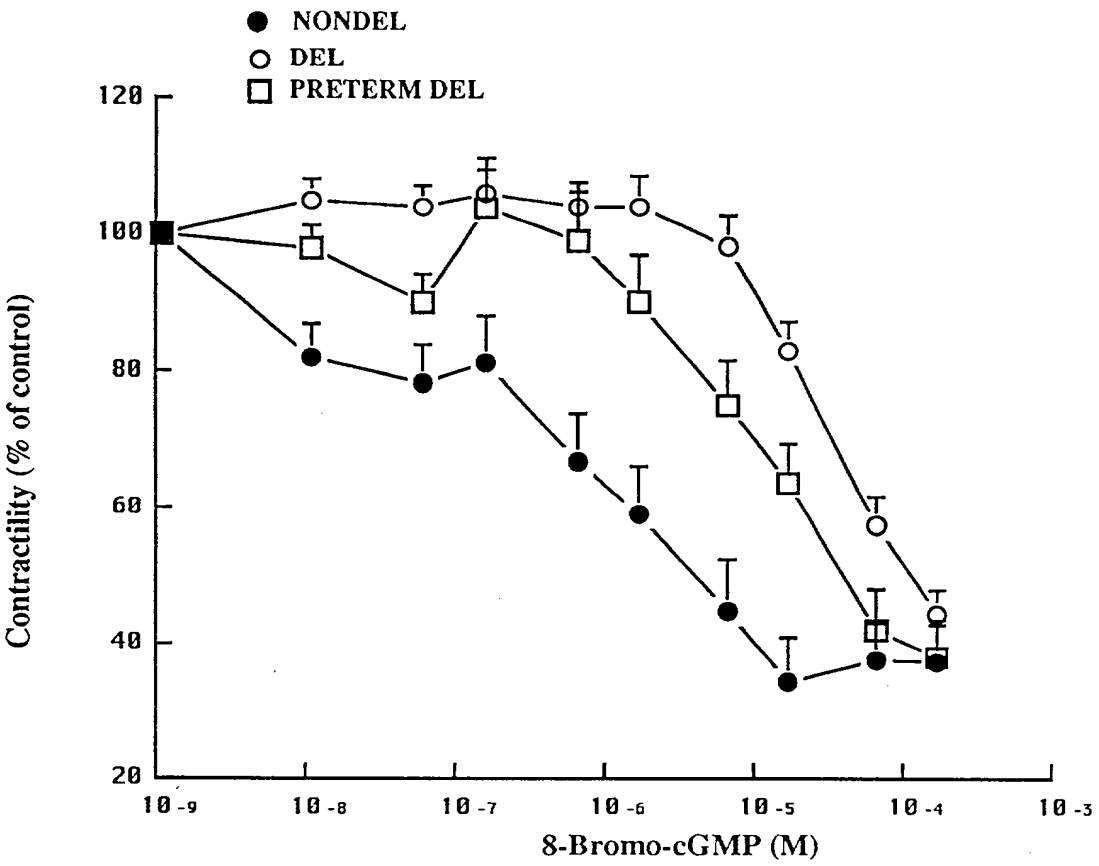
NONDEL
DEL
PRETERM DEL
120
100
80
60
40
20
Contractility (% of control)
10 -9
10 -8
10 -7
10 -6
10 -5
10 -4
10 -3
8-Bromo-cGMP (M)

Figure 4

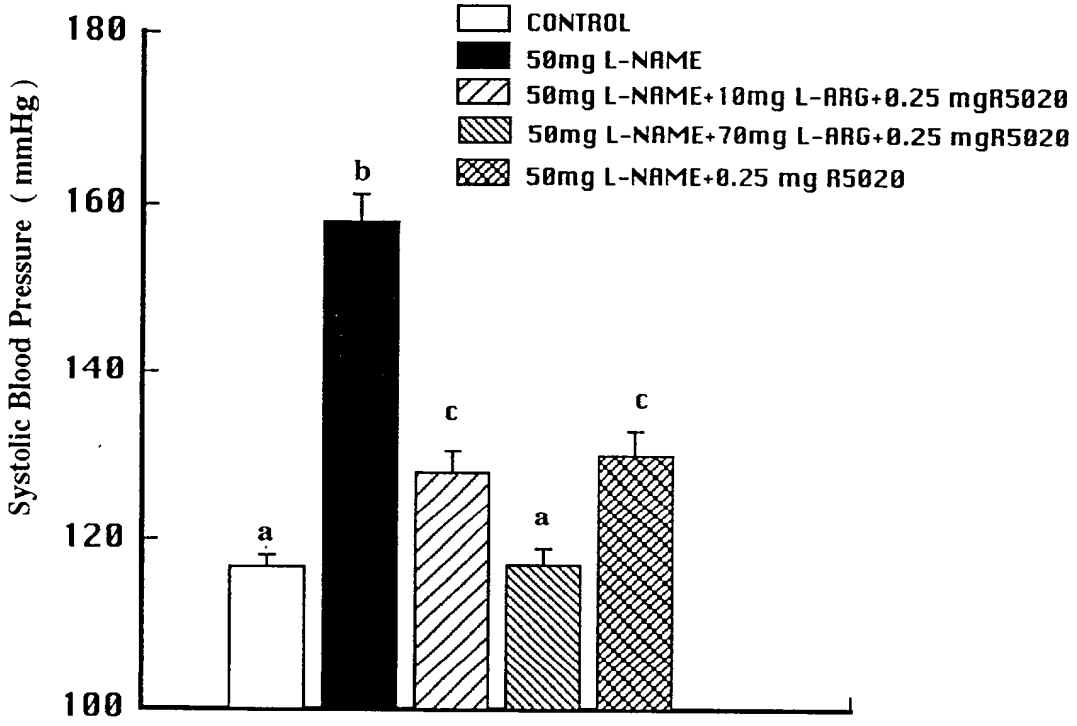
CONTROL
50mg L-NAME
50mg L-NAME+10mg L-ARG+0.25 mgR5020
50mg L-NAME+70mg L-ARG+0.25 mgR5020
50mg L-NAME+0.25 mg R5020
Systolic Blood Pressure (mmHg)
180
160
140
120
100
a
b
c
a
c

Figure 5

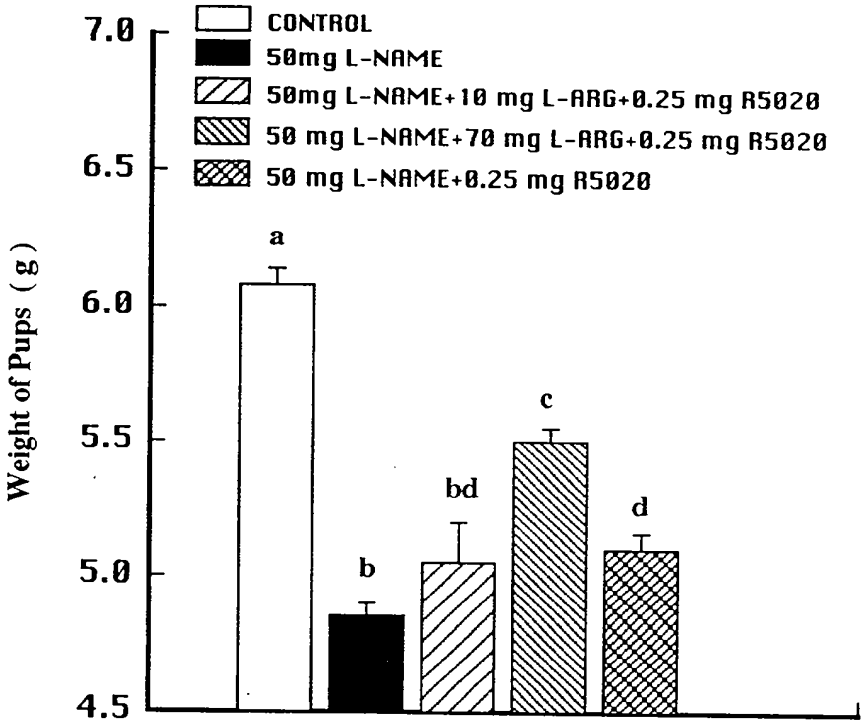
CONTROL
50mg L-NAME
50mg L-NAME+10 mg L-ARG+0.25 mg R5020
50 mg L-NAME+70 mg L-ARG+0.25 mg R5020
50 mg L-NAME+0.25 mg R5020
Weight of Pups (g)
7.0
6.5
6.0
5.5
5.0
4.5
a
b
bd
c
d

Figure 6

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY
(Includes Reference to PCT International Applications)

ATTORNEY'S DOCKET NUMBER
SCH 1237

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

TREATMENT OF PREECLAMPSIA, TOXEMIA AND PRETERM LABOR WITH COMBINATION OF PROGESTATIONAL AGENT AND A NITRIC OXIDE SYNTHASE SUBSTRATE AND/OR DONOR

the specification of which (check only one item below):

☐ is attached hereto.

☒ was filed as United States application

Serial No. 08/092,426

on July 16, 1993,

and was amended

on _____ (if applicable).

☐ was filed as PCT international application

Number _____

on _____,

and was amended under PCT Article 19

on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowlege the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

COUNTRY (if PCT, indicate "PCT")	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 USC 119
			☐ YES ☐ NO
			☐ YES ☐ NO

Combined Declaration For Patent Application and Power of Attorney (Continued)

(Includes Reference to PCT International Applications)

ATTORNEY'S DOCKET NUMBER: SCH 1237

207	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY
208	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY
209	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY
210	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY
211	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY
212	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF INVENTOR 201	DATE	SIGNATURE OF INVENTOR 207	DATE
Robert E Garfield	24 Sept '93		
SIGNATURE OF INVENTOR 202	DATE	SIGNATURE OF INVENTOR 208	DATE
SIGNATURE OF INVENTOR 203	DATE	SIGNATURE OF INVENTOR 209	DATE
SIGNATURE OF INVENTOR 204	DATE	SIGNATURE OF INVENTOR 210	DATE
	24 Sept, 93		
SIGNATURE OF INVENTOR 205	DATE	SIGNATURE OF INVENTOR 211	DATE
SIGNATURE OF INVENTOR 206	DATE	SIGNATURE OF INVENTOR 212	DATE

Combined Declaration For Patent Application and Power of Attorney (Continued)
(Includes Reference to PCT International Applications)

ATTORNEY'S DOCKET NUMBER: SCH 1237

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

U.S. APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED

PCT APPLICATION NO.	PCT FILING DATE	U.S. SERIAL NUMBERS ASSIGNED (if any)			

POWER OF ATTORNEY: As a named inventor, I hereby appoint I. William Millen (19,544); John L. White (17,746); Anthony J. Zelano (27,969); Alan E. J. Branigan (20,565); John R. Moses (24,983); Harry B. Shubin (32,004); Brion P. Heaney (32,542); Diana Hamlet-King (33,302); Richard J. Traverso (30,595); Richard E. Kurtz (33,936); John A. Sopp (33,103) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

Send Correspondence to: MILLEN, WHITE, ZELANO AND BRANIGAN, P.C.
Arlington Courthouse Plaza I, Suite 1400
2200 Clarendon Boulevard
Arlington, Virginia 22201

Telephone No. 703-243-6333

Direct Telephone Calls to:

201	FULL NAME OF INVENTOR	FAMILY NAME: GARFIELD	FIRST GIVEN NAME: Robert	SECOND GIVEN NAME: E.
	RESIDENCE & CITIZENSHIP	CITY: Friendswood	STATE OR FOREIGN COUNTRY: Texas	COUNTRY OF CITIZENSHIP: U.S.A.
	POST OFFICE ADDRESS	STREET: 1814 Winding Way	CITY: Friendswood	STATE & ZIP CODE/COUNTRY: TX 77546 U.S.A.
202	FULL NAME OF INVENTOR	FAMILY NAME: CHWALISZ	FIRST GIVEN NAME: Krzysztof	SECOND GIVEN NAME:
	RESIDENCE & CITIZENSHIP	CITY: D-1000 Berlin 27	STATE OR FOREIGN COUNTRY: Germany	COUNTRY OF CITIZENSHIP: Germany
	POST OFFICE ADDRESS	STREET: Lobber Steig 7a	CITY: D-1000 Berlin 27	STATE & ZIP CODE/COUNTRY: Germany
203	FULL NAME OF INVENTOR	FAMILY NAME: BUKOWSKI	FIRST GIVEN NAME: Radoslaw	SECOND GIVEN NAME:
	RESIDENCE & CITIZENSHIP	CITY: D-1000 Berlin 27	STATE OR FOREIGN COUNTRY: Germany	COUNTRY OF CITIZENSHIP: Poland
	POST OFFICE ADDRESS	STREET: c/o K. Chwalisz Lobber Steig 7a	CITY: D-1000 Berlin 27	STATE & ZIP CODE/COUNTRY: Germany
204	FULL NAME OF INVENTOR	FAMILY NAME: YALLAMPAL LI	FIRST GIVEN NAME: Chandra	SECOND GIVEN NAME:
	RESIDENCE & CITIZENSHIP	CITY: Houston	STATE OR FOREIGN COUNTRY: Texas	COUNTRY OF CITIZENSHIP: India
	POST OFFICE ADDRESS	STREET: 1222 Berkeley Lake	CITY: Houston	STATE & ZIP CODE/COUNTRY: TX 77062 U.S.A.
205	FULL NAME OF INVENTOR	FAMILY NAME:	FIRST GIVEN NAME:	SECOND GIVEN NAME:
	RESIDENCE & CITIZENSHIP	CITY:	STATE OR FOREIGN COUNTRY:	COUNTRY OF CITIZENSHIP:
	POST OFFICE ADDRESS	STREET:	CITY:	STATE & ZIP CODE/COUNTRY:
206	FULL NAME OF INVENTOR	FAMILY NAME:	FIRST GIVEN NAME:	SECOND GIVEN NAME:
	RESIDENCE & CITIZENSHIP	CITY:	STATE OR FOREIGN COUNTRY:	COUNTRY OF CITIZENSHIP:
	POST OFFICE ADDRESS	STREET:	CITY:	STATE & ZIP CODE/COUNTRY:

COPY

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY
(Includes Reference to PCT International Applications)

ATTORNEY'S DOCKET NUMBER
SCH 1237

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

TREATMENT OF PREECLAMPSIA, TOXEMIA AND PRETERM LABOR WITH COMBINATION OF PROGESTATIONAL AGENT AND A NITRIC OXIDE SYNTHASE SUBSTRATE AND/OR DONOR

the specification of which (check only one item below):

☐ is attached hereto.

☒ was filed as United States application

Serial No. 08/092,426

on July 16, 1993,

and was amended

on _____ (if applicable).

☐ was filed as PCT international application

Number _____

on _____,

and was amended under PCT Article 19

on _____ (if applicable).

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PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

COUNTRY (if PCT, indicate "PCT")	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 USC 119
			☐ YES ☐ NO
			☐ YES ☐ NO
			☐ YES ☐ NO
			☐ YES ☐ NO

Combined Declaration For Patent Application and Power of Attorney (Continued)
(Includes Reference to PCT International Applications)

ATTORNEY'S DOCKET NUMBER: SCH 1237

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U.S. APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED

PCT APPLICATION NO.	PCT FILING DATE	U.S. SERIAL NUMBERS ASSIGNED *(if any)*			

POWER OF ATTORNEY: As a named inventor, I hereby appoint I. William Millen (19,544); John L. White (17,746); Anthony J. Zelano (27,969); Alan E. J. Branigan (20,565); John R. Moses (24,983); Harry B. Shubin (32,004); Brion P. Heaney (32,542); Diana Hamlet-King (33,302); Richard J. Traverso (30,595); Richard E. Kurtz (33,936); John A. Sopp (33,103) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

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Combined Declaration For Patent Application and Power of Attorney (Continued)

(Includes Reference to PCT International Applications)

ATTORNEY'S DOCKET NUMBER: SCH 1237

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	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY
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	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY
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	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	STREET	CITY	STATE & ZIP CODE/COUNTRY

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF INVENTOR 201	DATE	SIGNATURE OF INVENTOR 207	DATE
SIGNATURE OF INVENTOR 202	DATE 10/09/93	SIGNATURE OF INVENTOR 208	DATE
SIGNATURE OF INVENTOR 203	DATE 4/10/93	SIGNATURE OF INVENTOR 209	DATE
SIGNATURE OF INVENTOR 204	DATE	SIGNATURE OF INVENTOR 210	DATE
SIGNATURE OF INVENTOR 205	DATE	SIGNATURE OF INVENTOR 211	DATE
SIGNATURE OF INVENTOR 206	DATE	SIGNATURE OF INVENTOR 212	DATE